53 Lung function, weight, and sweat chloride responses in patients with cystic fibrosis and the *G551D-CFTR* mutation treated with ivacaftor: A secondary analysis

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Clinical studies show improved FEV_1 in ivacaftor-treated CF patients with the *G551D-CFTR* mutation when compared with placebo. To better understand the clinical benefit for those who fall below the median response, we examined pharmacodynamic and efficacy data from Phase 3 ivacaftor Studies 102/103.

This secondary analysis of patients who received 48 weeks of ivacaftor (n = 109) or placebo (n = 100), examined the number needed to treat (NNT), frequency and cumulative distribution functions and subset analyses to evaluate response (sweat chloride, FEV_1, weight). Changes in these outcomes according to FEV_1 response were also compared.

The NNT for a reduction in sweat chloride of 20 mMol/L was 1.03. To achieve an improvement in FEV_1 of ⩾5%, NNT was 1.73. For both treatment populations, the data were normally distributed with a shift toward benefit for the ivacaftor group. Numerical differences were seen in sweat chloride and weight for ivacaftor-treated patients, regardless of whether or not a ⩾5% FEV_1 improvement was achieved (Table).

Ivacaftor was observed to produce an effect on sweat chloride, FEV_1, and weight. These analyses indicate that in % predicted FEV_1 responders (⩾5% improvement) and minimal responders (<5% improvement) weight gain and change in sweat chloride are similar.

Table 1

Measure	Mean change in FEV_1 % predicted <5%				Mean change in FEV_1 % predicted ⩾5%			
	Study 102		Study 103		Study 102		Study 103	
	Δ I (n = 22) vs. P (n = 64)	*P* value	Δ I (n = 10) vs. P (n = 18)	*P* value	Δ I (n = 61) vs. P (n = 12)	*P* value	Δ I (n = 16) vs. P (n = 6)	*P* value
% predicted FEV_1, %	4.2	<0.0001	1.6	0.5093	6.2	0.0023	9.8	0.0522
[Sweat chloride], mMol/L	−46.1*	<0.0001	−55.8**	<0.0001	−49.7†	<0.0001	−53.9‡	<0.0001
Body weight, kg	3.3	<0.0001	2.0	0.0582	1.7	0.3313	3.4	0.0094

*Data available for 20 (ivacaftor) and 61 (placebo) patients. **Data available for 9 (ivacaftor) and 17 (placebo) patients. †Data available for 58 (ivacaftor) and 11 (placebo) patients. ‡Data available for 14 (ivacaftor) and 5 (placebo) patients.

54 UK and Ireland review of ivacaftor in severe CF: Impact on hospitalisations and antibiotic use

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Objectives: Clinical trials of ivacaftor in CF patients carrying the G551D gene mutation have shown improvements in FEV_1, weight and the risk of pulmonary exacerbation. However, no reduction in the number of exacerbations requiring intravenous (IV) antibiotic treatment or hospitalisation was seen. These trials excluded patients with severe CF (FEV_1 <40% predicted), for whom exacerbations and hospitalisations are more frequent events. We aimed to assess the impact of ivacaftor on exacerbation frequency and antibiotic days in G551D patients with severe CF (FEV_1 <40%).

Methods: 9 CF centres with severe CF patients on compassionate-use ivacaftor in the UK and Ireland took part. Clinical data were recorded for 1 year prior and a minimum of 3 months post Ivacaftor commencement. The use of antibiotics was deemed a surrogate for exacerbations. Post-ivacaftor events were normalised to rates per year for analysis.

Results: 16 patients (7 male) received ivacaftor for a median 185 days. Following Ivacaftor, mean (±sd) rates of antibiotic courses per subject fell from 6.2 (±3.0) to 3.5 (±3.4) per year (p = 0.008). Courses of in-hospital antibiotics similarly decreased from a median of 3 to 0.73 per year (p = 0.029). Median (IQR) number of IV antibiotic days reduced from 73 (46–109) to 32 (4–68) days per year, p = 0.0024. Median hospital IV days fell from 28 (13–76) to 4 (0–33) days per year (p = 0.006).

Conclusions: Ivacaftor significantly reduces exacerbation frequency, hospitalisation rates and in-patient days in CF patients with severe lung function impairment. This study supports the use of ivacaftor in a patient population which have been previously excluded from clinical trials.

55 Reliability of intestinal current measurement as CFTR biomarker and responsiveness to oral ivacaftor treatment

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Objectives: CFTR modulators are an attractive strategy for mutation-specific CF therapy. Results of recent clinical trials pointed to possible differences in organ specificity and drug efficacy, raising questions about the choice of the best CFTR biomarkers. ICM, determining CFTR function in human rectal biopsies, showed excellent discriminative validity. Aim of this study was to evaluate intra-individual variability and reliability (within-subject repeatability) of ICM, and to assess responsiveness to oral ivacaftor treatment.

Methods: ICM was repetitively performed (ECFS ICM SOP) on 3 consecutive time points (baseline, after 1 & 2 weeks) in each of 10 subjects (mean age 33.6 years, range 18–53): 4 PI-CF patients, 3 PS-CF patients and 3 healthy controls. A total of 240 rectal suction biopsies (8/subject per day) was included. Mean, SD and CV were calculated. Two F508del/G551D-patients started oral treatment with CFTR modulator ivacaftor directly after ICM at baseline, and responsiveness after 1 and 2 weeks were measured.

Conclusion: For all ICM parameter intra-individual variability between biopsies of the same day was low. Repetitive ICMs showed repeatable results in >95% of data. In vivo treatment with ivacaftor normalised rectal CFTR function to levels of non-CF control.

These first data on reliability of ICM demonstrate a low biological intra-subject variation and a high responsiveness to in vivo Ivacaftor treatment. Clinical trials evaluating the long-term correlation of ICM to surrogate parameters can facilitate the transition of ICM to a potential new surrogate parameter in CF drug development.

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56 Effect of withdrawal of ivacaftor therapy on CFTR channel activity and lung function in patients with cystic fibrosis

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Ivacaftor, a CFTR potentiator, improved CFTR channel activity and lung function in patients with CF and the *G551D-CFTR* mutation. Phase 3 studies showed durability of drug response; however, they provided no information on durability following ivacaftor withdrawal.

Three randomized, blinded, Phase 2 studies in G551D patients had cross-over designs, enabling analysis of sweat chloride and clinical markers both during ivacaftor therapy and following withdrawal. Ivacaftor treatment lasted 14 days in Study 101, and 28 days in Studies 106/107. All studies measured sweat chloride and FEV_1. Additional measures included lung clearance index (LCI) in 106 and MRI using hyperpolarized gas in 107. Decreases in sweat chloride and improvements in absolute FEV_1 % predicted were observed during treatment with ivacaftor in all 3 studies (Table). Following ivacaftor withdrawal (ranging from 7–28 days), sweat chloride and FEV_1 returned to near baseline (Table).

In this analysis with a limited sample, the effects of ivacaftor on CFTR channel activity and lung function were maintained during treatment and returned to near baseline within 7–28 days following ivacaftor withdrawal, suggesting that continued therapy is required to sustain improved CFTR activity and lung function.

Study	N	Mean (SE) change from baseline through end of ivacaftor treatment	*P* value within group	Ivacaftor treatment duration (days)	Mean (SE) change from baseline through drug washout	*P* value within group	Time since last ivacaftor dose (days)
Sweat chloride (mmol/L)							
101	3	−54.8 (7.5)	*	14	+7.2 (3.5)	*	7–28
106	16	−49.0 (3.9)	<0.0001	28	−4.0 (2.0)	0.0707	28
107	8	−45.2 (4.2)	0.0078	28	+0.4 (4.0)	0.7422	14
Absolute percent predicted FEV_1							
101	4	+5.2 (2.0)	*	14	+1.9 (2.4)	*	7–28
106	18**	+7.1 (2.7)	0.0104	28	−1.9 (2.3)	0.7819	28
107	8	+8.8 (2.7)	0.0313	28	−2.1 (2.0)	0.3125	14